Claims

1. A method of treating a neoplasm characterized by abnormally high levels of tyrosine kinase activity in a patient in need thereof, said method comprising administering to said patient at least one mTOR inhibitor together or in parallel with at least one tyrosine kinase inhibitor in amounts effective to treat said neoplasm.

2. The method of claim 1, wherein said mTOR inhibitor is a rapamycin macrolide.

3. The method of claim 1, wherein said rapamycin macrolide is rapamycin, CCI-779, Everolimus, or ABT-578.

4. The method of claim 1, wherein said said tyrosine kinase inhibitor is selected from the group consisting of a small molecule inhibitor, an antibody, an antisense oligomer, and an RNAi inhibitor.

5. The method of claim 4, wherein said small molecule inhibitor is selected from the group consisting of Imatinib, SU101, ZD1839, OSI-774, CI-1033, SU5416, SU6668, ZD4190, ZD6474, PTK787, PKI166, GW2016, EKB-509, EKB-569, CEP-701, CEP-751, PKC412, SU11248, and MLN518.

6. The method of claim 4, wherein said antibody is selected from the group consisting of trastuzumab, C225, rhu-Mab VEGF, MDX-H210, 2C4, MDX-447, IMC-1C11, EMD 72000, RH3, and ABX-EGF.

7. The method of claim 1, further comprising administering an MEK inhibitor.

8. The method of claim 7, wherein said MEK inhibitor is selected from PD184352, PD198306, PD98059, UO126, Ro092210, and L783277.

9. The method of claims 1-8, wherein said neoplasm is selected from carcinoma of the bladder, breast, colon, kidney, liver, lung, head and neck, gall-bladder, ovary, pancreas, stomach, cervix, thyroid, prostate, or skin; a hematopoietic tumor of lymphoid lineage; a hematopoietic tumor of myeloid lineage; a tumor of mesenchymal origin; a tumor of the central or peripheral nervous system; melanoma; seminoma; teratocarcinoma; osteosarcoma; thyroid follicular cancer; and Kaposi's sarcoma.

10. The method of claim 9, wherein said hematopoietic tumor of lymphoid lineage is selected from leukemia, acute lymphocytic leukemia, acute lymphoblastic leukemia, B-cell lymphoma, T-cell-lymphoma, Hodgkin's lymphoma, non-Hodgkin's lymphoma, hairy cell lymphoma and Burkett's lymphoma.

11. The method of claim 9, wherein said hematopoietic tumor of myeloid lineage is selected from acute myelogenous leukemia, chronic myelogenous leukemia, multiple myelogenous leukemia, myelodysplastic syndrome and promyelocytic leukemia.

12. The method of claim 9, wherein said tumor of mesenchymal origin is fibrosarcoma or rhabdomyosarcoma.

13. The method of claim 9, wherein said tumor of the central or peripheral nervous system is selected from astrocytoma, neuroblastoma, glioma and schwannomas

14. The method of claims 2 or 3, wherein said tyrosine kinase activity is epidermal growth factor receptor activity; said neoplasm is selected from non-small-cell lung cancer, breast cancer, ovarian cancer, bladder cancer, prostate cancer, salivary gland cancer, pancreatic cancer, endometrial cancer, colorectal cancer, kidney cancer, head and neck cancer, and glioblastoma multiforme; and said tyrosine kinase inhibitor is selected from the group consisting of SU101, ZD1839, OSI-774, CI-1033, PKI166, GW2016, EKB-509, EKB-569, trastuzumab, C225, MDX-H210, 2C4, MDX-447, and ABX-EGF.

15. The method of claims 2 or 3, wherein said tyrosine kinase activity is human epidermal growth factor receptor-2 activity; said neoplasm is selected from the group consisting of breast cancer, ovarian cancer, bladder cancer, salivary gland cancer, endometrial cancer, pancreatic cancer, and non-small-cell lung cancer; and said tyrosine kinase inhibitor is selected from the group consisting of CI-1033, GW2016, trastuzumab, MDX-H210, MDX-447, ABX-EGF, EMD 72000, RH3, and 2C4.

16. The method of claim 15, wherein said tyrosine kinase inhibitor is trastuzumab.

17. The method of claims 2 or 3, wherein said tyrosine kinase activity is platelet derived growth factor receptor activity; said neoplasm is selected from the group consisting of gastrointestinal stromal tumor, small cell lung cancer, glioblastoma multiforme, and prostate cancer; and said tyrosine kinase inhibitor is selected from the group consisting of Imatinib, SU101, MLN518, and PTK787.

18. The method of claim 18, wherein said wherein said tyrosine kinase inhibitor is Imatinib.

19. The method of claims 2 or 3, wherein said tyrosine kinase activity is Flt-3 activity; said neoplasm is acute myeloid leukemia and said tyrosine kinase inhibitor is selected from MLN518, SU11248, and PKC412.

20. The method of claim 19, wherein said tyrosine kinase inhibitor is PKC412.

21. The method of claims 2 or 3, wherein said tyrosine kinase activity is tropomyosin receptor kinase activity; said neoplasm is prostate cancer or pancreatic cancer; and said tyrosine kinase inhibitor is Imatinib, CEP701 or CEP705.

22. The method of claims 2 or 3, wherein said tyrosine kinase activity is BCR/ABL activity; said neoplasm is chronic myelogenous leukemia or acute lymphoblastic leukemia; and said tyrosine kinase inhibitor is Imatinib.

23. The method of claims 2 or 3, wherein said tyrosine kinase is a vascular endothelial growth factor receptor kinase; said cancer is any solid tumor; and said tyrosine kinase inhibitor is selected from the group consisting of SU5416, SU6668, ZD4190, ZD6474, PTK787, IMC-1C11, and rhu-Mab VEGF.

24. The method of claims 1, 14, 15, 17, 18, 19, 21, 22, or 23, wherein said neoplasm is resistant to said tyrosine kinase inhibitor.

25. The method of claims 14, 15, 17, 18, 19, 21, 22, 23, or 24, further comprising administration of an MEK kinase inhibitor.

26. The method of claim 25, wherein said MEK inhibitor is selected from PD184352, PD198306, PD98059, UO126, Ro092210, and L783277.

27. The method of claim 1, wherein said mTOR inhibitor and said tyrosine kinase inhibitor are administered in parallel within 30 days of each other.

28. The method of claim 27, wherein said rapamycin macrolide and said tyrosine kinase inhibitor are administered in parallel within 5 days of each other.

29. The method of claim 28, wherein said rapamycin macrolide and said tyrosine kinase inhibitor are administered in parallel within 24 hours of each other.

30. The method of claim 1, wherein said rapamycin macrolide and said tyrosine kinase inhibitor are administered together.

31. The method of any of claims 27-30, further comprising administration of an MEK kinase inhibitor.

32. The method of claim 31, wherein said MEK inhibitor is selected from PD184352, PD198306, PD98059, UO126, Ro092210, and L783277.

33. A method of treating leukemia in a patient in need thereof, said method comprising administering rapamycin to said patient in amounts effective to treat said leukemia.

34. A method of treating a neoplasm in a patient in need thereof, said method comprising administering to said patient at least one mTOR inhibitor together or in parallel with at least one tyrosine kinase inhibitor and at least one MEK inhibitor in amounts effective to treat said neoplasm.

35. The method of claim 34, wherein said neoplasm is selected from carcinoma of the bladder, breast, colon, kidney, liver, lung, head and neck, gall-bladder, ovary, pancreas, stomach, cervix, thyroid, prostate, or skin; a hematopoietic tumor of lymphoid lineage; a hematopoietic tumor of myeloid lineage; a tumor of mesenchymal origin; a tumor of the central or peripheral nervous system; melanoma; seminoma; teratocarcinoma; osteosarcoma; thyroid follicular cancer; and Kaposi's sarcoma.

36. The method of claims 34 or 35, wherein said mTOR inhibitor is selected from rapamycin, CCI-779, Everolimus, and ABT-578.

37. The method of claims 34 or 35, wherein said tyrosine kinase inhibitor is selected from Imatinib, SU101, ZD1839, OSI-774, CI-1033, SU5416, SU6668, ZD4190, ZD6474, PTK787, PKI166, GW2016, EKB-509, EKB-569, CEP-701, CEP-751, PKC412, SU11248, MLN518, trastuzumab, C225, rhu-Mab VEGF, MDX-H210, 2C4, MDX-447, IMC-1C11, EMD 72000, RH3, and ABX-EGF.

38. The method of claims 34 or 35, wherein said MEK inhibitor is selected from PD184352, PD198306, PD98059, UO126, Ro092210, and L783277.

39. Use of an mTOR inhibitor and a tyrosine kinase inhibitor in the manufacture of a medicament for the treatment of a neoplasm in a patient in need thereof, wherein said neoplasm is characterized by abnormally high levels of tyrosine kinase activity.

40. The use according to claim 39, wherein said mTOR inhibitor is a rapamycin macrolide selected from rapamycin, CCI-779, Everolimus, and ABT-578.

41. The use according to claims 39 or 40, wherein said tyrosine kinase activity is epidermal growth factor receptor activity; said neoplasm is selected from non-small-cell lung cancer, breast cancer, ovarian cancer, bladder cancer, prostate cancer, salivary gland cancer, pancreatic cancer, endometrial cancer, colorectal cancer, kidney cancer, head and neck cancer, and glioblastoma multiforme; and said tyrosine kinase inhibitor is selected from the group consisting of SU101, ZD1839, OSI-774, CI-1033, PKI166, GW2016, EKB-509, EKB-569, trastuzumab, C225, MDX-H210, 2C4, MDX-447, and ABX-EGF.

42. The use according to claims 39 or 40, wherein said tyrosine kinase activity is human epidermal growth factor receptor-2 activity; said neoplasm is selected from the group consisting of breast cancer, ovarian cancer, bladder cancer, salivary gland cancer, endometrial cancer, pancreatic cancer, and non-small-cell lung cancer; and said tyrosine kinase inhibitor is selected from the group consisting of CI-1033, GW2016, trastuzumab, MDX-H210, MDX-447, ABX-EGF, EMD 72000, RH3, and 2C4.

43. The use according to claims 39 or 40, wherein said tyrosine kinase activity is platelet derived growth factor receptor activity; said neoplasm is selected from the group consisting of gastrointestinal stromal tumor, small cell lung cancer, glioblastoma multiforme, and prostate cancer; and said tyrosine kinase inhibitor is selected from the group consisting of Imatinib, SU101, MLN518, and PTK787.

44. The use according to claims 39 or 40, wherein said tyrosine kinase activity is Flt-3 activity; said neoplasm is acute myeloid leukemia and said tyrosine kinase inhibitor is selected from MLN518, SU11248, and PKC412.

45. The use according to claims 39 or 40, wherein said tyrosine kinase activity is tropomyosin receptor kinase activity; said neoplasm is prostate cancer or pancreatic cancer; and said tyrosine kinase inhibitor is CEP701 or CEP705.

46. The use according to claims 39 or 40, wherein said tyrosine kinase activity is BCR/ABL activity; said neoplasm is chronic myelogenous leukemia or acute lymphoblastic leukemia; and said tyrosine kinase inhibitor is Imatinib.

47. The use according to claims 39 or 40, wherein said tyrosine kinase is a vascular endothelial growth factor receptor kinase; said cancer is any solid tumor; and said tyrosine kinase inhibitor is selected from the group consisting of SU5416, SU6668, ZD4190, ZD6474, PTK787, IMC-1C11, and rhu-Mab VEGF.

48. Use of an mTOR inhibitor, tyrosine kinase inhibitor, and MEK inhibitor in the manufacture of a medicament for the treatment of a neoplasm.

49. The use according to claim 48, wherein said neoplasm is selected from carcinoma of the bladder, breast, colon, kidney, liver, lung, head and neck, gall-bladder, ovary, pancreas, stomach, cervix, thyroid, prostate, or skin; a hematopoietic tumor of lymphoid lineage; a hematopoietic tumor of myeloid lineage; a tumor of mesenchymal origin; a tumor of the central or peripheral nervous system; melanoma; seminoma; teratocarcinoma; osteosarcoma; thyroid follicular cancer; and Kaposi's sarcoma.

50. The use according to claims 48 or 49, wherein said mTOR inhibitor is selected from rapamycin, CCI-779, Everolimus, and ABT-578.

51. The use according to claims 48 or 49, wherein said tyrosine kinase inhibitor is selected from Imatinib, SU101, ZD1839, OSI-774, CI-1033, SU5416, SU6668, ZD4190, ZD6474, PTK787, PKI166, GW2016, EKB-509, EKB-569, CEP-701, CEP-751, PKC412, SU11248, MLN518, trastuzumab, C225, rhu-Mab VEGF, MDX-H210, 2C4, MDX-447, IMC-1C11, EMD 72000, RH3, and ABX-EGF.

52. The use according to claims 48 or 49, wherein said MEK inhibitor is selected from PD184352, PD198306, PD98059, UO126, Ro092210, and L783277.

53. A pharmaceutical pack comprising an mTOR inhibitor and a tyrosine kinase inhibitor.

54. The pharmaceutical pack of claim 53, wherein said mTOR inhibitor and said tyrosine kinase inhibitor are formulated separately and in individual dosage amounts.

55. The pharmaceutical pack of claims 53 or 54, further comprising an MEK inhibitor.

56. The pharmaceutical pack of any of claims 53-55, wherein said mTOR inhibitor is a rapamycin macrolide selected from rapamycin, CCI-779, Everolimus, and ABT-578.

57. The pharmaceutical pack of any of claims 53-55, wherein said tyrosine kinase inhibitor is selected from Imatinib, SU101, ZD1839, OSI-774, CI-1033, SU5416, SU6668, ZD4190, ZD6474, PTK787, PKI166, GW2016, EKB-509, EKB-569, CEP-701, CEP-751, PKC412, SU11248, MLN518, trastuzumab, C225, rhu-Mab VEGF, MDX-H210, 2C4, MDX-447, IMC-1C11, EMD 72000, RH3, and ABX-EGF.

58. The pharmaceutical pack of any of claims 53-55, wherein said MEK inhibitor is selected from PD184352, PD198306, PD98059, UO126, Ro092210, and L783277.

59. A pharmaceutical composition comprising an effective amount of a rapamycin macrolide and a tyrosine kinase inhibitor, together with a pharmaceutically acceptable carrier or diluent.

60. The pharmaceutical composition of claim 56, further comprising an MEK inhibitor.

61. The pharmaceutical composition of claims 59 or 60, wherein said mTOR inhibitor is a rapamycin macrolide selected from rapamycin, CCI-779, Everolimus, and ABT-578.

62. The pharmaceutical composition of claims 59 or 60, wherein said tyrosine kinase inhibitor is selected from Imatinib, SU101, ZD1839, OSI-774, CI-1033, SU5416, SU6668, ZD4190, ZD6474, PTK787, PKI166, GW2016, EKB-509, EKB-569, CEP-701, CEP-751, PKC412, SU11248, MLN518, trastuzumab, C225, rhu-Mab VEGF, MDX-H210, 2C4, MDX-447, IMC-1C11, EMD 72000, RH3, and ABX-EGF.

63. The pharmaceutical composition of claims 59 or 60, wherein said MEK inhibitor is selected from PD184352, PD198306, PD98059, UO126, Ro092210, and L783277.

64. A method of determining whether a neoplasm in a human patient responds to a combination comprising an mTOR inhibitor and tyrosine kinase inhibitor, said method comprising the steps of:

a) administering said combination to said human patient; and

b) monitoring said patient to determine whether said neoplasm responds to said combination.

65. The method of claim 64, wherein said combination further comprises an MEK inhibitor.

66. The method of claims 64 or 65, wherein said neoplasm is selected from carcinoma of the bladder, breast, colon, kidney, liver, lung, head and neck, gall-bladder, ovary, pancreas, stomach, cervix, thyroid, prostate, or skin; a hematopoietic tumor of lymphoid lineage; a hematopoietic tumor of myeloid lineage; a tumor of mesenchymal origin; a tumor of the central or peripheral nervous system; melanoma; seminoma; teratocarcinoma; osteosarcoma; thyroid follicular cancer; and Kaposi's sarcoma.

67. The method of any of claims 64-66, wherein said mTOR inhibitor is selected from rapamycin, CCI-779, Everolimus, and ABT-578.

68. The method of any of claims 64-66, wherein said tyrosine kinase inhibitor is selected from Imatinib, SU101, ZD1839, OSI-774, CI-1033, SU5416, SU6668, ZD4190, ZD6474, PTK787, PKI166, GW2016, EKB-509, EKB-569, CEP-701, CEP-751, PKC412, SU11248, MLN518, trastuzumab, C225, rhu-Mab VEGF, MDX-H210, 2C4, MDX-447, IMC-1C11, EMD 72000, RH3, and ABX-EGF.

69. The method of any of claims 64-66, wherein said MEK inhibitor is selected from PD184352, PD198306, PD98059, UO126, Ro092210, and L783277.

70. The method of claims 64 or 65, wherein said neoplasm is characterized by abnormally high levels of tyrosine kinase activity.

71. The method of claims 64 or 65, wherein said mTOR inhibitor and said tyrosine kinase inhibitor are administered in parallel within 30 days of each other.

72. The method of claim 71, wherein said rapamycin macrolide and said tyrosine kinase inhibitor are administered in parallel within 5 days of each other.

73. The method of claim 72, wherein said rapamycin macrolide and said tyrosine kinase inhibitor are administered in parallel within 24 hours of each other.

74. The method of claims 64 or 65, wherein said rapamycin macrolide and said tyrosine kinase inhibitor are administered together.

75. The method of claim 65, wherein said MEK inhibitor is administered together with said tyrosine kinase inhibitor or said MEK inhibitor.

76. Use of an mTOR inhibitor and a tyrosine kinase inhibitor in the preparation of a medicament for determining whether a neoplasm in a human patient responds to a combination comprising an mTOR inhibitor and tyrosine kinase inhibitor, said method comprising the steps of:

a) administering said combination to said human patient; and

b) monitoring said patient to determine whether said neoplasm responds to said combination.

77. Use of an mTOR inhibitor, a tyrosine kinase inhibitor, and an MEK inhibitor in the preparation of a medicament for determining whether a neoplasm in a human patient responds to a combination comprising an mTOR inhibitor, tyrosine kinase inhibitor, and MEK inhibitor, said method comprising the steps of:

a) administering said combination to said human patient; and

b) monitoring said patient to determine whether said neoplasm responds to said combination.

78. Use according to claims 76 or 77, wherein said neoplasm is selected from carcinoma of the bladder, breast, colon, kidney, liver, lung, head and neck, gall-bladder, ovary, pancreas, stomach, cervix, thyroid, prostate, or skin; a hematopoietic tumor of lymphoid lineage; a hematopoietic tumor of myeloid lineage; a tumor of mesenchymal origin; a tumor of the central or peripheral nervous system; melanoma; seminoma; teratocarcinoma; osteosarcoma; thyroid follicular cancer; and Kaposi's sarcoma.

79. Use according to any of claims 76-78, wherein said mTOR inhibitor is selected from rapamycin, CCI-779, Everolimus, and ABT-578.

80. Use according to any of claims 76-78, wherein said tyrosine kinase inhibitor is selected from Imatinib, SU101, ZD1839, OSI-774, CI-1033, SU5416, SU6668, ZD4190, ZD6474, PTK787, PKI166, GW2016, EKB-509, EKB-569, CEP-701, CEP-751, PKC412, SU11248, MLN518, trastuzumab, C225, rhu-Mab VEGF, MDX-H210, 2C4, MDX-447, IMC-1C11, EMD 72000, RH3, and ABX-EGF.

81. Use according to any of claims 76-78, wherein said MEK inhibitor is selected from PD184352, PD198306, PD98059, UO126, Ro092210, and L783277.

82. Use according to claims 76 or 77, wherein said neoplasm is characterized by abnormally high levels of tyrosine kinase activity.

83. Use according to claims 76 or 77, wherein said mTOR inhibitor and said tyrosine kinase inhibitor are administered in parallel within 30 days of each other.

84. Use according to claim 83, wherein said rapamycin macrolide and said tyrosine kinase inhibitor are administered in parallel within 5 days of each other.

85. Use according to claim 84, wherein said rapamycin macrolide and said tyrosine kinase inhibitor are administered in parallel within 24 hours of each other.

86. Use according to claims 76 or 77, wherein said rapamycin macrolide and said tyrosine kinase inhibitor are administered together.

87. Use according to claim 77, wherein said MEK inhibitor is administered together with said tyrosine kinase inhibitor or said MEK inhibitor.

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